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Cystinuria is a rare but very interesting disease. Its chief interest is from the point of view of body metabolism and the various careful studies of this disease have added much to our knowledge of protein katabolism. The treatment of the disease has received but little consideration.

Cystinuria has a definite symptom-complex and may be readily diagnosed. The symptoms are those of renal stone, and differ but little from those of other types of renal-stone disease. Certain features, however, are somewhat characteristic.

1. The stones are usually very small. They are sharp edged, rough, with a color and texture very similar to that of a small piece of maple sugar.

2. The stones tend to occur in the urine in showers, usually after a period of high protein ingestion.

3. The amount of blood in the urine is often out of proportion to the symptoms and to the size and number of stones.

The diagnosis of cystinuria is readily made by microscopic examination of the urine. Cystin appears in the form of flat hexagonal crystals. These are insoluble in weak acids, but are readily soluble in weak alkalies.

The treatment has been almost entirely dietary. Alsberg and Folin[1] in a striking piece of work, proved that the amount of cystin excreted in the urine, in a case of cystinuria, varied directly with the amount of protein consumed. They do not believe that there are different degrees of severity of the disease but that the amount of cystin excreted depends on the amount of protein consumed, plus the protein katabolized from the wear and tear on body tissues. For this reason it is not possible to get the urine of a cystinuric free from crystals. On a diet which contained practically no protein, the amount of cystin excreted was very small. At the end of thirteen days, however, the patient was not cystin-free.

The practical application of these facts in the treatment of cystinuria is self-evident. The patients should be kept on a low nitrogenous

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1. Alsberg and Folin: Am. Jour. Physiol., 1905, xiv, 54.

diet. In the subsequent treatment of their patient, Folin was able by these means, to keep him free from symptoms for over a year. Most patients, however, chafe under the restrictions of a low protein diet, and are willing even to suffer from renal colic, rather than bear the monotony of the nitrogen-poor regimen. Furthermore 30 to 50 gm. of protein a day is minimum for normal metabolism, and this amount causes a considerable excretion of cystin.

Cystin is so readily soluble in weak alkali, that it seemed plausible to treat cystinuria by the addition of sodium bicarbonate to the diet. This empirical treatment only needed a patient for its justification. Curiously enough two of these cases were studied at about the same time and treated by the same method, one by Klemperer and Jacoby[2] in Berlin and one by myself. The report of Klemperer's case, however, was published in March, 1914, and since this treatment was similar to mine, though my conclusions are at variance from his, it was thought advisable to defer publishing my studies for a year, meanwhile keeping the patient under observation.

Klemperer's patient had a typical history and symptom-complex. The studies are briefly reported. The patient was first placed on a rich protein diet. No estimation of the nitrogen intake or of the urinary nitrogen is recorded. The cystin both precipitated and in solution was determined by Gaskell's[3] method. They found a total of 716 mg. of cystin on the fifth day of the high protein diet.

The patient was then put on a very low protein diet for three days. The average excretion of cystin was 78 mg. This they called the "endogenous cystin." Finally a mixed diet was given. The nitrogen intake or excretion is not stated. From 6 to 10 gm. of sodium bicarbonate were added to the diet each day. The cystin both in the precipitate and in solution rapidly decreased and on the fifth day none was present in the urine. These results are very striking, and their conclusions are that the alkali does not act as a solvent for cystin, but actually influences metabolism of the body so that cystin is not excreted or even formed.

The patient studied by us had a characteristic history.

Patient 812, a white printer, unmarried, aged 22, was entered as complaining of gravel present in the urine for twenty months.

Family History.—The patient's father is living and is said to have tabes dorsalis. His mother, one brother and three sisters are living and well. No tuberculosis, cancer, diabetes or kidney trouble occur in the family. He denies venereal disease. He uses a moderate amount of tea, coffee and tobacco, but no alcohol.

Past History.—Patient's health has always been poor. He had scarlet fever with a cardiac complication at an early age. At 8 years of age he had rheumatic

2. Klemperer and Jacoby: Therap. d. Gegenw., 1914, lv, 101.
3. Gaskell, J. F.: Jour. Physiol., London, 1907, xxxvi, 142.

fever and chorea and was ill for eight or nine months. Rheumatic fever recurred every spring for two or three years. Two years ago he was operated on at the Boston City Hospital for appendicitis and inguinal hernia and made a satisfactory convalescence.

Present Illness.—Six months after the operation the patient passed a small stone in the urine. This was soon followed by many others. Several patent medicines were tried, without relief. In August, 1913, the patient went to the Boston City Hospital with complete anuria, which he said had existed for three days. He was in the hospital three days, during which time he passed no urine. Being of a stubborn and intractable disposition, he refused cystoscopy or operation. He was discharged against advice and walked home. On the journey, "something gave way" and during the day he passed over "a gallon" of urine. The patient was seen by us first in January, 1913, when he came to the Peter Bent Brigham Hospital outdoor department. His chief symptoms then were pain in the lower lumbar region, pain over the symphysis pubis and blood and gravel in the urine.

Physical Examination.—The patient's weight was 110 pounds; he was poorly developed, though fairly well nourished. The heart was slightly hypertrophied, with a high-pitched systolic murmur at the apex. The abdomen showed slight tenderness in the costovertebral angle on both sides. No abdominal masses or tenderness were made out. Examination otherwise was negative. The urine showed large numbers of typical cystin crystals and a small amount of blood, but no casts. Blood pressure was normal, hemoglobin, 95 per cent., and white blood cell count, 10,000.

The patient was admitted to the house for metabolic study Jan. 31, 1914. The following data was recorded: intake of fluid, intake of nitrogen, output of urine, specific gravity of urine, the reaction of the urine as measured by the hydrogen ionization method, output of total nitrogen, urea, uric acid, ammonia, total sulphates and inorganic sulphates. (The results are shown in the table.)

The hydrogen ionization was determined according to the colorimetric method of Henderson and Palmer.[4] The factor 7.4 represents the reaction point of blood, the most alkaline figure, 8.4, is definitely pink to phenolphthalein. The diet was standardized by Locke's[5] tables. The urinary nitrogen, urea, uric acid and ammonia were determined by the microchemical methods of Folin[6] and his associates. The total sulphates and inorganic sulphates were determined by the method of Folin.

Alsberg and Folin[1] have shown that cystin is best quantitated by the determination of neutral sulphur. Ethereal sulphur was not determined since it remains constant. On 119 gm. protein intake the normal average excretion of ethereal sulphur as SO_3 is 0.22 gm. in twenty-four hours. The normal average of neutral sulphur as SO_3 is 0.17 gm. In cystinuria there is a marked increase in the neutral sulphur, which is due to the sulphur of cystin.

The patient was put on a standard diet containing 10.5 gm. of nitrogen. He remained on this diet two days before the records were begun. His blood examination showed:

Nonprotein nitrogen	28.0 mg. per 100 c.c. of blood
Urea nitrogen	14.0 mg. per 100 c.c. of blood
Uric acid	1.4 mg. per 100 c.c. of blood
Creatinin	1.2 mg. per 100 c.c. of blood
Creatin	10.0 mg. per 100 c.c. of blood

The creatinin and creatin determinations were made by Dr. W. Denis.

On February 5, 2 gm. of cystin were given to the patient. This was excreted at once as inorganic sulphur, substantiating the observation of Alsberg and Folin,

4. Henderson and Palmer: Jour. Biol. Chem., 1912, xiii, 363.
5. Locke: Food Values, New York, D. Appleton & Co., 1911.
6. Folin, O.: Jour. Biol. Chem., 1912, xi, 493.

RESULTS OF URINE EXAMINATION IN PATIENT WITH CYSTINURIA

Date	Intake Fluid, c.c.	Volume Urine, c.c.	Sp. Gr.	Hydrogen Ioniz.	Total Nitrogen, Gm.		Urea N	Ammonia N	Uric Acid	Total Sulphur as SO_3	Inorganic SO_3	Undetermined SO_3	Remarks
					Intake	Output							
2/3/14	3,000	710	1.023	7.3	10.5	10.56	8.02	0.334	0.72	1.78	1.14	0.64	Standard diet
2/4/14	1,950	1,020	1.020	7.4	10.5	11.52	8.68	0.234	0.50	1.89	1.19	0.69	Standard diet
2/5/14	1,650	810	1.023	7.2	10.5	10.87	8.78	0.319	0.31	2.73	1.98	0.75	Plus 2 gm. cystin.
2/6/14	2,100	970	1.020	7.2	10.5	10.24	8.69	0.313	0.45	1.70	1.09	0.61	Standard diet
2/7/14	1,900	1,550	1.024	8.2	10.5	10.47	9.39	0.540	0.56	1.98	1.08	0.90	Standard diet and 40 gm. sodium bicarbonate
2/8/14	1,750	1,660	1.021	8.4	10.5	9.50	8.10	0.506	0.55	1.64	0.907	0.73	Standard diet and 40 gm. sodium bicarbonate

that cystin is katabolized, and not absorbed and excreted unchanged. On the 7th, 40 gm. of sodium bicarbonate were added to the diet. This was repeated on the 8th. This treatment was followed by a slight increase in the neutral cystin sulphur, rather than a decrease, as noted by Klemperer. The striking thing that occurred, however, was that despite the increase in cystin sulphur, cystin crystals at once disappeared from the urine. This could be due to but one thing, namely, alkalinity of the urine.

Klemperer states that in his case cystin disappeared from the urine both in the precipitate and in solution; in our case the cystin simply went into solution. It seems hardly reasonable to suppose that sodium bicarbonate can influence body metabolism since Henderson[7] has shown that even very large amounts of alkali added to the blood do not influence its reaction. It has been suggested that in Klemperer's case, the cystin was present in the urine, but was in solution, and the method used did not detect it in the presence of the alkali.

The results from giving 40 gm. of sodium bicarbonate were definite and satisfactory, but needless to say, a patient cannot take 40 gm. nor even 10 gm. of sodium bicarbonate every day without digestive and other disturbances. In a previous unpublished experiment on hydrogen ionization of the urine, we have found that it required from 8 to 12 gm. of sodium bicarbonate a day to keep the urine definitely alkaline, that is, below 7.4, when on a diet of from 10 to 12 gm. of nitrogen. The higher the total nitrogen, the more alkali required. The practical solution is obvious; a low nitrogen diet which will offer some variety, with small amounts of sodium bicarbonate to keep the urine alkaline.

Our patient declined to tolerate any further quantitative metabolic experiments, but it has been possible to follow him clinically. He was put on a 5 to 6 gm. nitrogen diet with 4 gm. of sodium bicarbonate a day, given some litmus paper and told to keep the urine at a point where the litmus always turned blue.

Subsequent History.—The patient reported at frequent intervals. Whereas he had been having all the symptoms of renal stones; colic, constant pain in the back radiating down to the groin, hematuria, etc., he was now entirely free from these symptoms. An occasional crystal could be found in the urinary sediment. He passed no stones until August when he broke his strict dietary rules eating large amounts of meat and fish. He passed 20 or 30 stones within two or three days, and suffered considerable pain and distress.

Following this period it was thought best to give the patient one protein day a week. The low nitrogen diet was taken every day but Friday. On this day he was given 10 or 12 gm. nitrogen together with from 12 to 14 gm. of sodium bicarbonate. The patient was better satisfied and free from symptoms.

In February, 1915, one year after the metabolic studies had been made, the patient was given 10 or 12 gm. of nitrogen a day for one week, without sodium bicarbonate. At the end of three days there was a return of all symptoms, with the passage of 50 to 75 small stones and showers of typical crystals in the urine.

The patient was then put on the regimen suggested by Klemperer, 10 to 14 gm. of nitrogen a day with 10 gm. of sodium bicarbonate a day. At the end of two weeks, cystin crystals were readily found in the urine, and an occasional small stone was passed; furthermore the large doses of bicarbonate were not well tolerated by the stomach. He voluntarily returned to the regimen of six low protein days and one moderate protein day. Beginning March 2, 1915, he was given a diet containing 10 to 12 gm. of nitrogen and 12 to 15 gm. of sodium bicarbonate. After five days the urine was found to be alkaline to litmus, with only an occasional cystin crystal in the sediment. Total cystin determined by a new colorimetric method in Dr. Folin's laboratory showed 0.6 to 0.7 gm. of cystin. This experiment furnishes conclusive evidence, that in our case at least, cystin is being excreted in such an amount as would be expected from the nitrogen intake, but is rendered soluble by the alkali.

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7. Henderson, L. J.: Jour. Biol. Chem., 1909, vi, 29.

CONCLUSIONS

1. Cystinuria is best treated by a low protein diet, with the addition of sufficient alkali to keep the urine alkaline.

2. Cystin crystals will practically disappear from the urine of a cystinuric when sufficient sodium bicarbonate is added to the diet to render the urine alkaline.

3. The amount of sodium bicarbonate necessary to render the urine alkaline, when the patient is on a nitrogen intake of 10 gm., or more, is greater than can be well borne by the stomach.

4. Sodium bicarbonate does not influence body metabolism in cystinuria but simply renders the cystin soluble.

I desire to thank Dr. Folin for his many helpful suggestions in this study.